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Research Article

A Triple-Blinded Randomized Study to Evaluate the Effect of Acetaminophen and Morphine Sulfate on Pain Relief in MI-patients

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ABSTRACT

Background: Myocardial infarction is considered to be the most common symptom of cardiovascular diseases. Regarding the limitation of access to Morphine sulphate as a special drug and complications followed, this study aims to compare the treatment effects of intravenous acetaminophen and morphine sulphate on the reduction of pain in MI patients and to improve the cardiac performance.

Methods: The present study is a triple-blind randomized control trial in which 70 patients were divided into two separated groups and the pain was measured using Visual Analogue Scale. All analysis was done using SPSS Software at the significance level of 5 percent.

Results: 42 patients were male (60%) of whom 20 were in case group and 22 in control group. There were no significant difference between intervention group and control group in terms of VAS score (p = 0.520). The index change of VAS over the time was statistically significant (p=0.001) in intervention and control groups (intra group change). The results of variance analysis with repeated measurements showed that mean differences of Ejection Fraction over time in both groups of intervention and control was not statistically significant (p=0.28).

Conclusion: The findings of this study demonstrate that although Acetaminophen does not have an improved effect on pain control and cardiac performance than Morphine sulphate, it can be still an appropriate alternative for Morphine sulfate due to the lack of destructive effects and its availability.

Cardiovascular disease (CVD) and especially coronary heart disease (CHD), are known to be one of the causes of mortality in developing and developed countries and based on the studies carried out, over 40% of death cases in Iran are related to CVD [1-2]. The rate of CHD incidence in Iran has been reported to be about 22% (22.2% in males and 18.8% in females) which is increasing due to the increase of life expectancy and ageing in Iran [3].

CHDs have different complications which represent as angina pectoris and myocardial infarction (MI). MI is referred to as the process in which the rupture of an atherosclerotic plaque causes thrombosis formation in coronary arteries leading to absence or reduction of myocardial blood flow, which threatens the patients` life in the fourth and fifth decade [4].

Chest pain (over 80% cases), dyspnea, diaphoresis and sometimes nausea and vomiting are the most common

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signs of MI which force the patients to refer to emergency departments [4-5].

The main part of treatment for MI is carried out in emergency ward, one of which is alleviating the pain by morphine sulfate (2 to 4 mg intravenous). There have been different protocols of treatment studied which have paid attention to the role of acetaminophen in pacifying and recovering the signs of MI in oral, injection and rectal form [6-7].

On the other hand, there are controversies on the destructive or preventive role of acetaminophen. Merrill et al. showed that acetaminophen leads to improvement of ventricular performance following re-perfusion, less structural abnormality, less ventricular arrhythmias, and reduction of free radical production [8-9].

On the other hand, some studies have reported an increase of mortality and cerebrovascular accident following the use of nonsteroidal anti-inflammatory drugs in MI patients while others did not report negative or positive effects of acetaminophen [10-13].

Alleviation of pain and anxiety in patients inflicted with MI plays an important role in treatment progress and can prevent the ischemic progress in myocardium.

As morphine sulfate is known to be an opioid, it can't be accessed easily and there are some limitations to use it; therefore, replacing it with a medicine such as acetaminophen which is easily available can be a giant leap in treatment if its positive effects are proved.

Most studies on acetaminophen effect have been done on animals and it is necessary to do a research on the effect of acetaminophen on pain reduction and the symptoms of MI patients while comparing its effects with those of opium as the most common treatment.

Methods

This study approved by the local ethics committee of Hamadan University of Medical Sciences is a triple-blinded randomized controlled trial (RCT) in which all patients of 40-80 years old referring to Farshchian hospital of Hamadan due to chest pain in the period of study were investigated and the MI diagnosis was provided for them with signs and electrocardiogram. The protocol was registered in the Iranian Registry of Clinical Trials (IRCT201405133954N7). In the checklist provided, the demographic information, (age and sex), pain score, blood pressure and heart rate in entry and 0.5, 1, 2, 4, 6, 12, 18 and 24 hours after MI were recorded.

The results of the third day and the sixth week echocardiography after MI were recorded in terms of ejection fraction (EF) (by Simpson method) and wall motion.

The exclusion criteria were systolic pressure less than 100 mmHg or more than 200 mmHg, diastolic pressure less than 60 mmHg , the history of MI, clinical heart failure, advanced renal and hepatic disease, opium addiction , visual analogue scales (VAS) greater than 3 (if the patients under treatment of acetaminophen had VAS greater than 3 or requested more analgesia (sedative), they received one dose of acetaminophen and were excluded from the study), loss of consciousness, requirement for fibrinolytic therapy or emergency revascularization.

Having been selected and explained the aims of project with consent, all patients received 3 mg morphine sulfate and were divided into two groups: The intervention group received 4 doses of intravenous acetaminophen (1gr intravenous every six hours dissolved in 100cc normal saline) and the control group received 3 mg morphine sulfate as patients requested. The pain rate was measured with VAS [14]. The rate of pain was described as painless=VAS 0, mild pain=VAS 1-3, moderate pain=VAS 4-6, severe pain=Vas 7-10.

Randomization:

70 dark colour packets on which numbers 1 to 70 were written were divided into two groups of 35 randomly. Within each packet, there was placed a card with letter A on it (treatment group of acetaminophen) and letter B (treatment group of morphine sulfate). All the packets were delivered to the third Co-Worker of the experiment.

Letter A and B placed in the packet was determined from the tables of random numbers in that 35 packets containing letter A and 35 containing B were provided.

When the first patient referred, the packet 1 was opened and the patient was placed in the group the card in the packet determined. Likewise, in the study, each patient deserving the inclusion criterion was placed in the specified group based on the packet number. The data related to assessment of pain, blood pressure, heart rate were extracted by the second contributor and the data of heart performance including EF and wall motion by the first contributor in triple blind form.

Statistical analysis:

The statistical analyses were done using descriptive and analytical statistics methods such as central indexes and skewness, T-Test ،Chi-Square Test ،Paired T-Test ، Mann-Whitney Test, Wilcoxon Signed Ranks Test, ANOVA and Repeated Measure ANOVA at the level 5%.

Results

In the present study, 70 patients referred to Farshchian hospital for MI were studied. 42 patients were male, 20 in case group and 22 in witness group. The results showed that there is no significant difference in the mean age of intervention and control group (P=0.871).

Other variables of the study are shown in Table 1 in terms of intervention and control group. The VAS mean score is shown in terms of the periods of the study but no

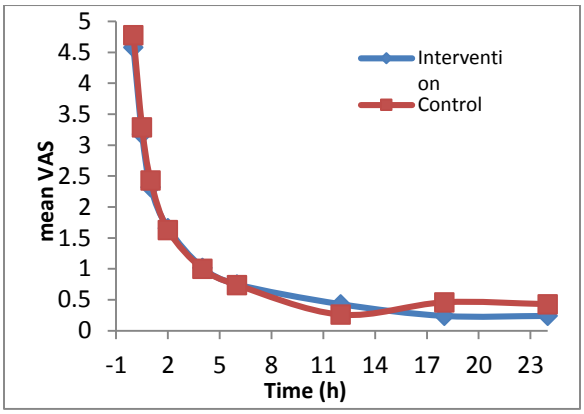
significant difference between two groups for VAS (P=0.520) (Figure 1).

Table 1- VAS, EF rate, blood pressure and heart rate data in the studied patients

Variable	Intervention (Sd+mean)	Control (Sd+mean)	P value
age	64.228±10.53	63.857±8.368	0.871
VAS			
total	1.501±0.506	1.584±0.559	0.520
At baseline	4.58±1.25	4.78±1.24	-
Half an hour later	3.18±1.07	3.29±1.09	-
One hour later	2.32±0.90	2.43±1.09	-
2 hours later	1.66±1.03	1.63±0.98	-
4 hours later	1.02±0.93	1±1	-
6 hours later	0.75±0.52	0.74±0.63	-
12 hours later	0.43±0.15	0.26±0.62	-
18 hours later	0.24±0.058	0.46±0.18	-
24 hours later	0.24±0.058	0.43±0.14	-
EF			
Total	42.2±8.28	44.27±7.59	0.280
Third day	42±7.82	44.2±7.38	-
42nd day	42.4±8.92	44.34±7.15	-
Diastolic blood pressure (total)	78.43±5.35	77.04±3.82	0.255
Systolic blood pressure (total)	132.710±7.62	129.597±8.28	0.255
Heart rate (total)	77.04±7.32	77.90±6.959	0.616

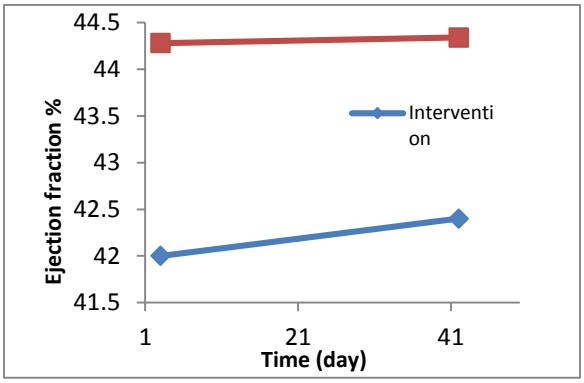
In this case, Friedman non-parametrical test showed that the trend VAS index change is statistically significant over time for intervention and control group (intra group change) (P=0.001).

Figure 1- Plot of VAS versus time in the patients studied



The result of variance analysis with repeated measurements showed that EF mean difference in control and witness is not statistically significant (P=0.28) (Table 1 and Figure 2).

Figure 2- Plot of VAS versus time in the patients studied



The mean of systolic and diastolic blood pressure was higher in intervention group than in control group but not statistically significant (p-value=0.255) (Figure 3-4).

Figure 3- Plot of diastolic blood pressure versus time in the patients studied

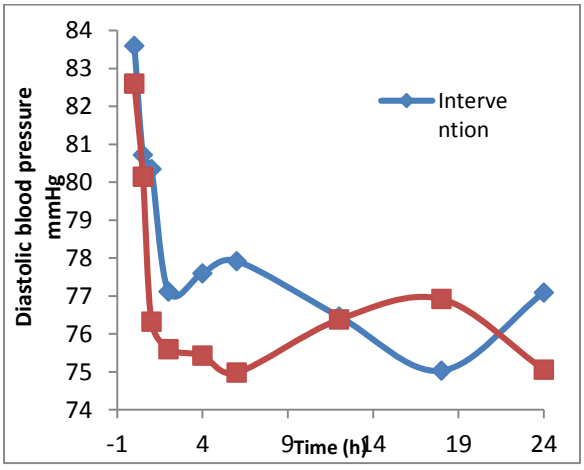
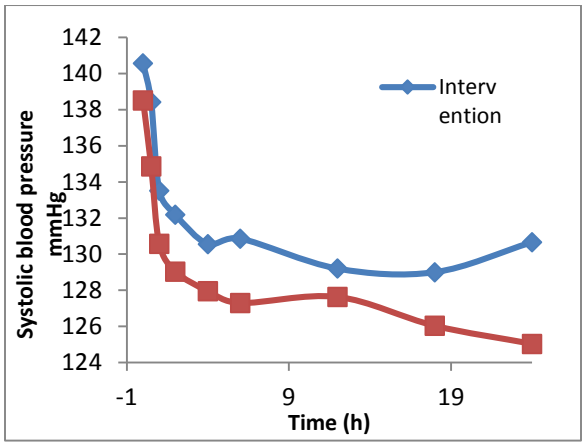
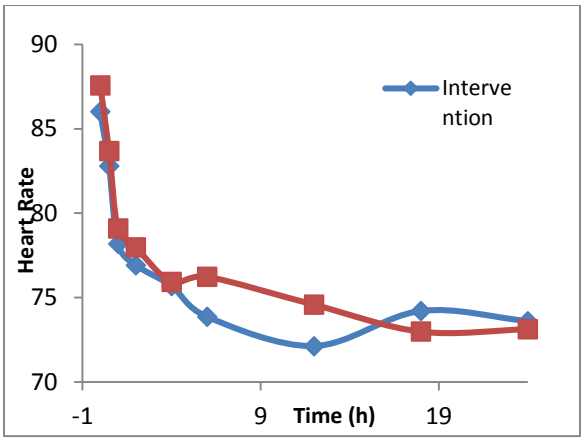


Figure 4- Plot of systolic blood pressure versus time in the patients studied



Yet, the trend of systolic and diastolic blood pressure change is statistically significant over time (P=0.001). Also, the trend of heart rate change within intervention and control group is statistically significant over time (p=0.000) while mean of this variable did not show any significant difference between groups (Figure 5).

Figure 5- Plot of heart rate versus time in the patients studied



The same finding was confirmed about the mean of involved segments in echocardiography in terms of hypokinesia, dyskinesia and akinesia and there was no significant difference between two groups (Table 2).

Table 2- Echocardiographic data at different times in the studied patients

Disorder type	Group	Third day	42-day	P value
Hypokinesia	case	4.43±1.94	3.86±2.24	0.018
	control	4.029±2.69	3.83±2.37	0.219
	P	0.51	0.863	-
Akinesia	case	1.41±0.94	1.42±0.83	0.285
	control	1.29±0.48	1.24±0.54	0.527
	P	0.073	0.364	-
Dyskinesia	case	0	0.34±0.057	0.367
	control	0	0.34±0.057	0.367
	P	1	1	-

Discussion

The increasing trend of cardiovascular diseases in developed and developing societies demands suitable treatments at first entry to hospital because, based on the predictions, by 2020 over 75% of all mortalities in Iran are from CVD and it is vital to present new suitable treatments to counteract the increasing incidence [15].

In this regard, for the first time, the application of acetaminophen and morphine sulfate as the most common medication to alleviate pain in patients inflicted with MI was compared while the results are subjects to some limitations due to other results in animal field. The findings showed that totally VAS mean in intervention group (acetaminophen) and control group (morphine

sulfate) did not have significant difference while over time the pain decreased in both groups. Different studies have paid attention to destructive or recovery effect of acetaminophen on cardiac performance to prevent MI or post MI angina and symptoms [8, 15-16].

In the present study, using echocardiography, we examined two important factors to compare the effect of acetaminophen and morphine sulfate: the amount of EF in the presence or absence of hypokinesia, dyskinesia or akinesia in patients.

Our findings showed that the mean EF and EF changes on the third day and sixth week in intervention and control group patients did not have significant difference. It can be said that although the difference of these two drugs in EF performance is not significant, regarding the slight increase of EF in both groups, they do not have the harmful effect on EF and do not reduce it.

In 2019, Charpentier et al. conducted the multi-center, randomized, non-inferiority cluster study comparing nitrous oxide/oxygen plus acetaminophen and morphine in patients with STEMI (ST Elevation Myocardial Infarction). According to the results of their study, oxide/oxygen plus acetaminophen is inferior to morphine analgesia in patients [17].

In 2016, Abdi and Basgut published an interesting study on pain management in acute myocardial infarction. In their study, they looked at the effects of using morphine derivatives in reducing pain and finding suitable alternatives [18]. In part of their study, they noted the analgesic and safety effects of acetaminophen. According to Graham et al. and Sin et al., acetaminophen has been widely used in Europe for the past two decades to reduce the pain of emergency patients [19-20].

Fulton et al. states concerns about the effect of acetaminophen on the incidence of cardiovascular diseases but his retrospective cohort study showed that using acetaminophen does not have any effect on the increased risk of cardiovascular diseases [11].

Leshnower et al. showed that acetaminophen leads to increase cardiac output and mean arterial pressure before ischemia in sheep but there is no effect on other hemodynamic parameters [7].

Merill et al. in an experimental study on the effect of acetaminophen on dogs` cardiac performance, showed that acetaminophen has antioxidant effect on myocardium and confirming the effect of drug on the recovery of cardiac performance [21].

Therefore, the results of our study, in contrast to those of other studies, do not show significant recovery in cardiac performance but as mentioned the methodological differences and the groups of comparison in animal and human studies have made it difficult to compare the results.

Our findings show that although acetaminophen does not have more and better effect on pain control and cardiac recovery performance than morphine sulfate, it can be a good alternative regarding lack of destructive effects and its availability.

It is suggested that the effect of acetaminophen and morphine sulfate is studied in greater scales of human studies and suitable methodologies so that best evidence-based treatment can be selected to alleviate pain and improve the cardiac performance of MI patients.

Conclusion

Our study results showed that there is no significant difference in pain control through using acetaminophen and morphine sulfate while both decreased the pain significantly over the time in patients. On the other hand, there was no difference in both groups in terms of cardiac performance recovery (upon echocardiography). Echocardiography did not show any difference in two groups statistically and both groups were similar and there was significant decrease of hypokinetic segments within intervention group while investigating mean of the involved segments as likely symptom, but there was no statistically significant difference between two groups. The general finding shows that acetaminophen works as effectively as morphine sulfate to control pain while lacking destructive effect.

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